PATENT
Attorney Docket No. **056291-5174-US**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **GELLERT *et al.***	)	
Application No.: **10/505,231**	)	Group Art Unit: **1615**
Filed: **August 19, 2004**	)	Examiner: Anderson, James D.
For: **PHARMACEUTICAL FORMULATION OF IRESSA COMPRISING A WATER-SOLUBLE CELLULOSE DERIVATIVE**	)	

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Window
Randolph Building
401 Dulany Street
Alexandria, VA 22314

November 1, 2006

Sir:

INFORMATION DISCLOSURE STATEMENT UNDER 37 C.F.R. § 1.97(c)

Applicant wishes to make of record the following circumstances regarding the controlled, confidential and non-commercial testing of a pharmaceutical composition falling within the scope of one or more of the present claims, which tests were carried out at least in part in the United States more than one year before the filing date of the present application as a part of clinical trials for the collection of data for presentation to the FDA during the regulatory review period preceding the approval of the drug Iressa (gefitinib tablets). It is Applicant's belief that the circumstances of this clinical testing are such that it does not constitute a "public use" or any other prior art event under 35 U.S.C. § 102. However, what are believed to be the relevant circumstances are presented below for completeness of the record and evaluation by the Examiner.

1. The invention as presently claimed is most broadly directed toward a pharmaceutical composition comprising the active drug gefitinib or a pharmaceutically acceptable salt

thereof, and a water-soluble cellulose ether or an ester of a water-soluble cellulose ether as set forth in the claims.

2. Gefitinib is the international non-proprietary (generic) name for the compound 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, as used in the present claims as "the Agent," which may also be expressed by the nomenclature 4-Quinazolinamine, N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-4-morpholin)propoxy] as set forth in the FDA approved label insert for Iressa. This active component is encompassed by claims of U.S. Patent No. 5,770,599 issued to Kieth Hopkinson Gibson on June 23, 1998 (hereinafter the "Gibson '599 patent").

3. The present specification acknowledges at page 1 that gefitinib is disclosed in published International Patent Application WO 96/33980 (corresponding to the Gibson '599 patent), and is now known as Iressa (registered trade mark), by way of the code number ZD 1839 and Chemical Abstracts Registry Number 184475-35-2. The Gibson '599 patent notes at column 13, beginning at line 13, that the disclosed compositions may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

4. However, certain characteristics of gefitinib make it prone to undesirable variability in the extent and/or rate of absorption between doses and between patients, possibility producing low or variable bioavailability. As detailed in the present specification at page 1, line 22 through page 2, line 29, gefitinib is a weakly basic compound having two basic

groups, and the protonation and deprotonation of these basic groups has a marked effect upon its solubility in aqueous media, being highly dependent upon pH. For example, the free-base form is soluble at pH 1 but is practically insoluble above pH 7, with a sharp drop off of solubility between pH 4 and pH 6.

5. Although gefitinib has a high solubility in the acidic environment of the stomach, it is not significantly absorbed in this area. The site of highest intrinsic absorption is thought to be in the upper intestine, but the pH is relatively high in this region of the GI tract compared to that in the stomach. Thus, gefitinib is prone to precipitate from solution as it passes from the acidic environment of the stomach to the higher pH environment of the upper GI tract, which results in reduced and/or variable absorption of gefitinib. In view of this particular pH sensitivity of gefitinib, even small variations in local pH may have a significant effect upon its pharmacokinetic profile. Even within a given patient, the pH of the GI tract can vary as a result of, for example, whether the patient is in a fed or fasted state and the rate of gastric emptying. This combination of a sensitive pH solubility profile and variability of the pH in the GI tract may result in a high degree variability in the bioavailability and/or plasma concentrations of gefitinib within a patient and between patients, and possibly sub-optimal treatment efficacy in a proportion of patients.

6. In brief chronology of relevant events leading to the present invention, the application leading to the Gibson '599 patent (claiming the active component *per se*) was filed in the United States on April 26, 1996 (claiming priority from a UK application filed April 27, 1995.

7. Prior to filing the IND (Investigational New Drug) application for Iressa (gefitinib tablets) with the FDA on November 17, 1997, oral tablet formulations containing gefitinib as the active ingredient were developed for use in the clinical trials. The effective date of the IND was December 17, 1997, after which the gefitinib tablets could, for the first, be tested in man. As shown in the Table of paragraph 14 below, the first clinical trial 1839IL/0005 that was conducted at least in part in the United States had a "1st subject in" date of April 29, 1998. The gefitinib formulations that were tested in that clinical trial and those that followed fell within the scope of the present claims

8. At some point within the time period of late 2001 to early 2002, Applicant found that the rate at which gefitinib is precipitated from solution, as the pH increases from that in the stomach to that in the upper GI tract, is reduced when gefitinib is formulated or administered together with certain excipients, specifically a water-soluble cellulose ether or an ester of a water-soluble cellulose ether as presently claimed. Priority applications were filed in the UK in early 2002 and the International Application disclosing and claiming this invention (from which the present application is the US National Stage) was filed on February 24, 2003.

9. Subsequent to commencement of clinical trials in April 1998 and prior to the February 24, 2003 effective US filing date of the subject application, additional clinical trials, as listed in the Tables of paragraphs 14, 19 and 22 below, were conducted at least in part in the United States with gefitinib tablets coming within the scope of the present claims. Clinical testing under the IND continued on behalf of AstraZeneca (formed by merger in 1999) until it was believed that sufficient evidence of safety and efficacy of the

formulation had been obtained, and the filing of the NDA (New Drug Application) for Iressa (gefitinib tablets) at the FDA was completed on August 5, 2002.

10. On May 5, 2003, the NDA was approved by the FDA for commercial marketing of Iressa (gefitinib tablets), specifically as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies. This was the first approval in the United States of any gefitinib formulation falling within the scope of the present claims. The gefitinib tablet formulation ultimately approved as Iressa is disclosed most specifically in Example 2 of the subject application, and comes within the composition scope of certain of the claims presently pending in this application.

11. The May 5, 2003 FDA approval date of the Iressa NDA constitutes the earliest possible date for commercial marketing in the United States of any gefitinib formulation coming within the scope of the present claims. Therefore, no composition within the scope of the present claims was (or could have been) on sale in the United States before the February 24, 2003 effective U.S. filing date of the present application.

12. Much of the testing of the gefitinib formulations was carried out abroad, but some of the clinical testing of these gefitinib formulation was carried out in the United States more than one year prior to the effective U.S. filing date of the present application, *i.e.*, prior to February 24, 2002. However, as will be evident below, all such testing that occurred in the United States prior to February 24, 2002 was carried out under clinical study agreements and related protocols which, *inter alia*, imposed obligations of confidentiality on the involved institutions and/or investigators with respect the composition of the

gefitinib formulation, gave AstraZeneca strict control over the permitted use and disposition of the drug product used in the trials, and imposed stringent requirements for a complete accounting for all drug product that was supplied and for the return or disposal of any drug product not used in the specified clinical trial. The agreements further provided that AstraZeneca was entitled to all information or data derived from the testing. Moreover, all persons enrolled in the clinical trials were advised of the experimental nature of the formulation, and acknowledged this in signed informed consent forms as a precondition to their enrollment, and were given the drug in bottles marked "investigational drug" and a label stating that the drug was only to be used for investigational purposes. AstraZeneca received no payment for the drug product, and was not otherwise compensated for the use of this drug product in the clinical trials. Under these conditions and the applicable case law discussed later below, these clinical trials of the gefitinib tablet formulation in the United States did not constitute a "public use" under 35 U.S.C. § 102(b) These tests did not place the formulation in the public domain or cause the public to believe that the formulation of the invention was freely available, and certainly did not constitute a commercial exploitation of the invention more than one year before the effective U.S. filing date of the suject application.

13. The trials that were carried out, at least in part, within the United States can be catagorized as "AstraZeneca Sponsored Trials," an "Expanded Access Trial" and "Investigator Sponsored Studies." These will be separately discussed below. Each trial was governed by a "Clinical Study Agreement" (or a "Confidentiality Agreement," in the case of the Expanded Access Trial), and the objectives and procedures to be followed by

the institution or investigator in carrying out a given trial was detailed in the "Protocol" for that trial. Additionally, the institution or investigator was provided a copy of the "Investigator's Brochure" for Iressa, which provided detailed information on the physical, chemical, and pharmaceutical properties and formulation of the drug substance and product; findings from the preceding nonclinical studies, including nonclinical pharmacology, pharmacokinetics and product metabolism in animals, and toxicology; effects in humans from earlier clinical trials, and a summary of data and guidance for the investigator. As relevant here, the **Investigator's Brochure** for Iressa described the constituents of the drug product as comprising ZD1839 as the active constituent, and as the excipients, the constituents set forth the following table:

Excipient		**Standard**
Tablet core		
Lactose monohydrate	:	Ph Eur
Cellulose microcrystalline	:	Ph Eur
Croscarmellose sodium	:	Ph Eur
Povidone	:	Ph Eur
Sodium lauryl sulphate	:	Ph Eur
Magnesium stearate	:	Ph Eur
Purified water	:	Ph Eur
Tablet coating		
Hypromellose (Methylhydroxypropylcellulose)	:	Ph Eur
Macrogol 300 (Polyethylene glycol 300)	:	Ph Eur
Red iron oxide	:	E172
Yellow iron oxide	:	E172
Titanium dioxide	:	Ph Eur
Purified water	:	Ph Eur

However, the cover page of the Investigator's Brochure is prominently marked:

"The information contained in this document is confidential and may not be reproduced or the contents disclosed, in whole or part, without the written authorization of AstraZeneca Pharmaceuticals."

AstraZeneca Sponsored Trials

14. The following table lists the AstraZeneca Sponsored Trials of ZD1839 that were carried out, at least in part, within the United States more than one year prior to the effective U.S. filing date of the subject application:

AstraZeneca Sponsored Trials				
Study No.	**Study Title**	**1st subject in**	**Last subject last visit**	**# of US patients (enrolled)**
1839IL/0005	1839IL/0005 - 14 day dose escalation	29-Apr-98	18-May-00	64
1839IL/0011	1839IL/0011 - 28 day dose escalation (US)	23-Dec-99	9-Aug-00	71
1839IL/0012	1839IL/0012 - 28 day dose escalation (ROW)	25-Feb-99	11-Aug-00	92
1839IL/0014	INTACT 1 - 1839IL/0014 - Pivotal ROW first line survival	12-Jul-00	31-Oct-01	128
1839IL/0017	INTACT 2 - 1839IL/0017 - Pivotal US first line survival	17-May-00	31-Oct-01	820
1839IL/0020	1839IL/0020 - Carbo/Taxol combination	6-Oct-99	16-Oct-01	25
1839IL/0021	1839IL/0021 - 5FU/LV Combination	1-Nov-99	9-Apr-01	26
1839IL/0023	1839IL/0023 - Estramustine combination	19-Feb-01	10-Apr-02	30
1839IL/0039	IDEAL 2 - 1839IL/0039 - Pivotal US monotherapy survival	13-Nov-00	22-Jan-02	221
1839IL/0040	1839IL/0040 - Iressa Monotherapy in HRPC	10-May-01	8-Oct-02	58

15. Each clinical study was carried out under a Clinical Study Agreement entered into by each Institution and/or Investigator taking part in the study.

16. A representative Clinical Study Agreement from Clinical Study 1839IL/0005 provided in part as here relevant:

16.1. **With respect to the Protocol:**

"The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol entitled "A Phase I, Multiple Rising Does Tolerance Trial of ZD1839

in Patients with Solid, Malignant Tumours" (hereinafter referred to as "Protocol") which is attached hereto as Exhibit A and incorporated herein by reference. Institution and Investigator shall use their best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith. Institution shall submit the Protocol for approval to the Human Subject Institutional Review Board (hereinafter "IRB"). Any modification to the Protocol must be mutually agreed to in writing by both parties and must, if appropriate, have the prior approval of Institution's IRB."

16.2. **With respect to the Study:**

"Zeneca shall provide, without cost to Institution, sufficient amounts of Product to Institution. Institution may not use Product in any way other than as specified in the Protocol."

16.3. **With respect to Termination:**

"Either party may terminate this Agreement and Study at any time in its sole discretion upon thirty (30) days prior written notice. However, Zeneca may terminate this Agreement and the Study upon five (5) days prior written notice for safety, regulatory or ethical reasons. In the event of termination, all unused Study materials shall be returned to Zeneca and Zeneca shall reimburse Institution and Investigator for all actual costs reasonably incurred up until the effective termination date."

16.4. **With respect to Ownership; Disclosure of Data; Publications:**

"(a) Institution will report results of the Study to Zeneca periodically and at the completion of the Study. All data and information in these reports and in the case report forms are the property of Zeneca to use any way it may see fit.

* * * * *

"(c) In order to effectively complete the Study, it may be necessary for the parties to disclose certain information considered proprietary or confidential (hereinafter "Confidential Information"). The parties agree to maintain in confidence all Confidential Information obtained relating to this Agreement and not to disclose any of said Confidential Information to a third party without the prior written consent of the other party. The disclosing party shall specify in writing the nature and identity of the Confidential Information and the manner and time of disclosure. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which is obtained from some third party not under any obligation to Zeneca or Institution with respect to such information, or (iv) information which Institution or Zeneca already have in their possession, prior to disclosure by the other party, as evidenced by written records.

"(d) Subject to the provisions of confidentiality set forth in Section 7(c) above, Investigator and Institution have the right to publish their findings in the

scientific literature, provided that Zeneca shall have the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Investigator and Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. In the event it is necessary for Zeneca to prepare a patent application(s) and other documentation, and upon request by Zeneca, Investigator and Institution agree to delay submission of such final draft manuscripts for publication for a period not exceeding three (3) months from the date on which Zeneca receives such final draft manuscripts. Investigator and Institution agree to implement any reasonable suggestions made to preserve Zeneca's right in its Confidential Information before any disclosure for publication or presentation. Investigator and Institution agree to take appropriate cognizance of any other suggestions by Zeneca before any disclosure for publication or presentation."

17. A representative Clinical Study Agreement from Clinical Study 1839IL/0011 provided in part as here relevant:

17.1. **With respect to the Protocol:**

"The clinical Study to be performed pursuant to this Agreement shall be that set forth in the Protocol which is attached hereto as Exhibit A and incorporated herein by reference. Institution and Investigator shall use their best efforts to ensure that the work required under the Protocol is properly performed in accordance therewith."

17.2. **With respect to Termination**

"AstraZeneca reserves the right to terminate this Agreement and Study at any time in its sole discretion upon five (5) days prior written notice. In the event of termination, all unused Study materials shall be returned to AstraZeneca and AstraZeneca shall reimburse Institution and Investigator for all actual costs reasonably incurred up until the effective termination date."

17.3. **With respect to Ownership; Disclosure of Date; Publications:**

"(a) All rights to all data, inventions or discoveries Institution and Investigator may make or conceive in the course of their work for AstraZeneca in their performance under this Agreement will be the property of AstraZeneca and will be assigned to AstraZeneca, and Institution and Investigator will assist AstraZeneca, at AstraZeneca's expense, by executing rightful papers for obtaining proper patent protection in such inventions or discoveries.

* * * * *

"(c) It may be necessary for AstraZeneca to disclose to Investigator and Institution certain information considered proprietary or confidential (hereinafter "Confidential Information") to aid Investigator and Institution in effecting or completing their performance under this Agreement. Confidential Information shall also include Study data; however, Investigator's and Institution's right to publish pursuant to Section (d) below shall not be affected by this provision. Investigator and Institution agree to maintain in confidence all Confidential

Information Investigator and Institution obtain from AstraZeneca relating to this Agreement and not to disclose any of said Confidential Information to a third party without the prior written consent of AstraZeneca. Notwithstanding the foregoing, it is understood that Confidential Information shall not include the following: (i) information that is now publicly available, (ii) information that later becomes publicly available, after it has become publicly available, (iii) information which Investigator and Institution obtain from some third party not under any obligation to AstraZeneca with respect to such information, or (iv) information which Investigator and Institution already have in their possession, prior to any disclosure by AstraZeneca, as evidenced by written records.

"Nothing herein shall prevent Investigator and Institution from complying with a legal obligation to disclose Confidential Information so long as Investigator and Institution (i) provide AstraZeneca prompt notice of its intent to disclose (or to resist disclosure) (ii) take reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) afford AstraZeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator and Institution have sought to resist disclosure) or obtain protection for the information disclosed.

"(d) Subject to the provisions of confidentiality set forth in Section 6(c) above, AstraZeneca agrees to grant Investigator and Institution the right to publish their findings in the scientific literature, provided that AstraZeneca shall have

the right to review, at least 30 days prior to submission for publication, copies of any and all final draft manuscripts which are authored or co-authored by Investigator and Institution or by anyone in their research group and which are based in whole or in part on research conducted under this Agreement. In the event it is necessary for AstraZeneca to prepare a patent application(s) and other documentation, and upon request by AstraZeneca, Investigator and Institution agree to delay submission of such final draft manuscripts for publication for a period not exceeding six (6) months from the date on which AstraZeneca receives such final draft manuscripts. Investigator and Institution agree to implement any reasonable suggestions made to preserve AstraZeneca's right in its Confidential Information before any disclosure for publication or presentation; Investigator and Institution agree to take appropriate cognizance of any other suggestions by AstraZeneca before any disclosure for publication or presentation."

18. A representative Clinical Study Agreement from Clinical Study 1839IL/0023

provided in part as here relevant:

18.1. **With respect to the Scope of Work:**

"Institution and its Principal Investigator shall conduct the clinical study entitled "A Pilot Trial of Escalating Doses of Oral ZDI839 (IRESSA^{TM}) in Combination with Docetaxel and Estrarmustine in Patients with Hormone-refractory Prostate Cancer" (the "Study") in accordance with this Agreement, Protocol Number 1839IL/0023 incorporated by reference herein and as may be amended (the "Protocol"), good

clinical and medical practice, and all applicable laws, rules, regulations and guidelines relating to the conduct of clinical investigations, including, without limitation, 21 CFR. Parts 50, 54, 56, and 312 (the "Applicable laws"). For purposes of this Agreement, the term "Institution" shall include the Principal Investigator and all other employees, executives, officers, directors, faculty, staff, and other authorized agents of Institution."

18.2. **With respect to Ownership and Control of Study Drug:**

"All Study Drug supplied to Institution shall remain the exclusive property of AstraZeneca until administered or dispensed to Subjects during the course of the Study. The Study Drug shall only be used as described in the Protocol in compliance with Applicable Laws. Upon termination or completion of the Study, Institution shall, at AstraZeneca's direction and expense, either return to AstraZeneca or dispose of any quantities of unused Study Drug, in accordance with AstraZeneca's instructions. Institution shall maintain complete and accurate records relating to the disposition of the Study Drug supplied to Institution."

18.3. **With respect to Confidential Information:**

"(a) For purposes of this Agreement, "Confidential Information" means any information of AstraZeneca identified as such, whether of a technical, business or other nature, including, but not limited to, information that relates to AstraZeneca's trade secrets, products, promotional material, developments, proprietary rights or business affairs, and any Inventions. Confidential Information does not include any information that:

"(i) Was known by Institution prior to disclosure by AstraZeneca, as can be shown by written documentation maintained in the ordinary course of business;

"(ii) Was lawfully obtained by Institution from a third party without any obligation of confidentiality, as can be shown by written documentation maintained in the ordinary course of business; or

"(iii) Is or becomes part of the public domain through no act or violation of any obligation of Institution and/or Principal Investigator, or

"(iv) Was independently developed by employees of Institution without access to the Confidential Information, as shown by written documentation maintained in the ordinary course of business.

"(b) For a period of seven (7) years after the expiration or termination of this Agreement, institution shall not, without AstraZeneca's prior written consent or as may be permitted by this Agreement, disclose to any third party any Confidential Information, and shall use such Confidential Information solely for purposes of performing its obligations under this Agreement. Institution shall restrict the dissemination of Confidential Information to only those persons within its organization who have a need to know, and shall apprise such persons of the obligation of confidentiality required by this Agreement, Institution and/or Principal Investigator shall use at least the same care and discretion in maintaining the confidentiality of the Confidential Information as it uses with its sensitive confidential information. Institution shall notify AstraZeneca immediately upon Institution's discovery of any loss or compromise of the Confidential Information.

Upon the termination or expiration of this Agreement or upon AstraZeneca's earlier request, Institution shall promptly return to AstraZeneca all Confidential Information, provided that Institution may retain copies of such Confidential Information required by law or regulation to be retained by Institution.

"(c) Notwithstanding subparagraph (b) above, if Institution is legally required to disclose Confidential Information, to the extent circumstances permit, Institution shall promptly notify AstraZeneca and consult with AstraZeneca on a mutually satisfactory way to disclose such information as necessary and in accordance with applicable law or regulation... Nothing contained herein shall prohibit Institution from immediately disclosing results of the Study to the extent necessary to prevent or mitigate a serious health hazard, provided, however, that, Institution shall use reasonable efforts to notify AstraZeneca prior to making such a disclosure, and shall in any case notify AstraZeneca immediately after it has made such a disclosure.

18.4. **With respect to Rights to Publication:**

"(a) Institution and Principal Investigator understand that the Study is being conducted as part of a multi-center clinical trial and that data from all centers will be pooled and analyzed. Subject to this Section, Institution and Principal Investigator may submit for publication any manuscript, abstract or other document, and present at any meeting, any data generated or arising from the performance of this Agreement after AstraZeneca or its designee publishes an article on the Study or after twelve (12) months have elapsed since the completion of the Study at all sites, whichever occurs first; provided, however, that neither Institution nor Principal Investigator may take

such action with respect to any publication or presentation, or portion thereof, which is in violation of Section 15, titled "Confidential Information" herein.

"(b) Institution and/or Principal Investigator shall submit a copy of any proposed manuscript, abstract, presentation or other document to AstraZeneca for review and comment and identification of any Confidential Information at least forty-five (45) days prior to its submission for publication or presentation. Upon the request of AstraZeneca, Confidential Information will be removed prior to publication or presentation. If requested in writing by AstraZeneca, Institution and/or Principal Investigator shall withhold material from submission for publication or presentation for an additional ninety (90) days to allow for the filing of a patent application or the taking of other measures to establish and preserve AstraZeneca's proprietary rights. To the extent that any provision of this Section 16 may be inconsistent in any respect with any statements about publication policy set forth in the Protocol, the provisions of this Section 16 shall control.

"(c) If either Institution or Principle Investigator publishes the results of the Study, AstraZeneca shall be granted an irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that Institution or Principal investigator may have. AstraZeneca also shall have the right to publish independently the results of the Study."

Expanded Access Trial

19. The following table identifies the Expanded Access Trial of ZD1839 that was carried out at least in part within the United States more than one year prior to the effective U.S. filing date of the subject application.

Expanded Access Trial				
Study No.	**Study Title**	**1st subject in**	**Last subject last visit**	**# of patients (enrolled)**
1839IL/0050	1839IL/0050 - Expanded Access	1-Sep-00	2-Sep-03	23387

20. The primary objective of the Expanded Access Trial (in times past sometimes referred to as a "Compassionate Use Trial") was to provide single agent ZD1839 to patients with advanced (inoperable stage III or IV) non-small cell lung cancer who have failed standard treatment, or patients who can not receive other systemic anticancer therapy, or patients who are not medically suitable for chemotherapy, or because of either unavailability or ineligibility for other clinical trials with ZD1839 (e.g., poor performance status, lack of geographic proximity). The trial was designed as a non-randomized, open-label, multi-center, expanded access clinical trial. The patients could receive ZD1839 as long as the physician feels that the patient is benefiting from this therapy without significant ZD1839 related toxicity, and safety information is provided regularly to AstraZeneca. The Protocol provided that treatment will be discontinued after ZD1839 becomes commercially available.

21. **A "Confidentiality Agreement" was entered into by each Investigator prior to his involvement in Clinical Study 1839IL/0050**, in which the Investigator acknowledged

that "he will have access to and obtain knowledge of certain proprietary and confidential Information of AstraZeneca and that as a condition of receiving such information" the parties agreed, in part as here relevant:

"1. 'Confidential Information' shall mean all information (a) disclosed by AstraZeneca, its affiliates or agents to Investigator, either orally, visually, in writing or by initiation of access to information as may be contained in a database or (b) obtained by the Investigator from a third party or any other source, regarding the business or affairs of AstraZeneca, its affiliates or agents, including but not limiting the generality of the foregoing, any information pertaining to IRESSA™ (ZD1839) and its use in clinical trials.

"Confidential Information shall not include information that: (i) was already in the possession of Investigator before disclosure thereof by AstraZeneca to the Investigator as evidenced by the Investigator's written records (ii) is independently developed by the Investigator as evidenced by the Investigator's written records, (iii) is or becomes publicly available through no fault of the Investigator, or (iv) is obtained by the Investigator from a third party under no obligation not to disclose same.

"Nothing herein shall prevent Investigator from complying with a legal obligation to disclose Confidential Information so long as Investigator (i) provides AstraZeneca prompt notice of his intent to disclose (or to resist disclosure) (ii) takes reasonable steps to require the recipient to preserve the confidential nature of the information once disclosed and (iii) affords AstraZeneca the opportunity to attempt to prevent the disclosure (whether or not Investigator has sought to resist disclosure) or obtain protection for the information disclosed.

"2. The purpose of the disclosure of Confidential Information is for the involvement of Investigator with the protocol 1839IL/0050 titled 'An Expanded Access Clinical Program with ZD1839 (IRESSA™) for Patients with Advanced Non-small Cell Lung Cancer (NSCLC)'.

"3. The Investigator agrees to maintain in strictest confidence and to take all reasonable steps to maintain the confidentiality of the Confidential Information for a period of ten (10) years from the date of disclosure of the Confidential Information to Investigator. The Investigator also agrees not to disclose Confidential Information to any third party, and to use Confidential Information only for the purposes stated in paragraph 2 of this Agreement.

"4. The Investigator recognizes that all documents and records received by the Investigator from AstraZeneca and all copies of such records and documents shall be AstraZeneca's property exclusively. The Investigator shall at all times keep all such documents, records and copies of documents and records in the Investigator's custody and subject to the Investigator's control and shall surrender the same upon request by AstraZeneca.

"5. The Investigator shall not disclose any Confidential Information to any of his employees, except employees of the Investigator who have a need to know the Confidential Information for the purposes stated in paragraph 2 of this Agreement and who have assumed an obligation to maintain AstraZeneca's Confidential Information in confidence at least to the extent that the Investigator is bound hereunder. The Investigator shall advise each such employee of the confidential nature of the Confidential Information received from AstraZeneca and of the existence and importance of the confidentiality provisions of this Agreement and shall be responsible for ensuring that such employees maintain the Confidential Information in confidence in accordance with the terms of this Agreement.

"6. Because of the unique nature of the Confidential Information, the Investigator understands and agrees that AstraZeneca will suffer irreparable harm in the event that the Investigator fails to comply with any of its obligations contained hereinabove and that monetary damages will be inadequate to compensate AstraZeneca for such breach. Accordingly, the Investigator agrees that AstraZeneca shall have the right to seek immediate injunctive relief to enforce the confidentiality obligations contained herein."

Investigator Sponsored Studies

22. The following table identifies Investigator Sponsored Studies of ZD1839 that were carried out, at least in part, within the United States more than one year prior to the effective U.S. filing date of the subject application.

Investigator Sponsored Studies (mainly NCI)				
Study No.	**Study Title**	**1st subject in**	**Last subject last visit**	**# of patients (enrolled)**
1839IL/0156	A NON-RANDOMIZED, OPEN-LABLE PHASE II, MULTI-CENTER TRIAL OF ZD1839 (IRESSATM) 500 MG DAILY IN PATIENTS WITH ADVANCED BREAST CANCER	5-Oct-01	29-Nov-02	63
1839IL/0161	A PHASE II TRIAL OF ZD1839 IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA	19-Jan-01	15-Apr-03	18
1839IL/0162	A PHASE II STUDY OF ZD1839 IN RENAL CELL CARCINOMA STAGE IV AND RENAL CELL CARCINOMA RECURRENT	30-Apr-01	31-Oct-02	21
1839IL/0164	A PHASE II STUDY OF ZD1839 IN NEWLY DIAGNOSED PATIENTS WITH GLIOBLASTOMA (GRADE 4 ASTRCYTOMA)	9-Mar-01	21-Apr-04	98
1839IL/0165	A PHASE III TRIAL OF CISPLATIN/ETOPSIDE/RADIOTHERAPY WITH CONSOLIDATION DOCETAXEL FOLLOWED BY MAINTENANCE THERAPY FOR ZD1839 OR PLACEBO IN PATIENTS WITH INOPERABLE LOCALLY ADVANCED STAGE III NSCLC	30-Jun-01	ongoing	492
1839IL/0166	A PHASE II STUDY OF ZD1839 IN RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK	2-Jul-01	ongoing	29
1839IL/0167	A PHASE II STUDY OF ZD1839 FOR PATIENTS WITH FIRST RELAPSE GLIOBLASTOMA MULTIFORME	23-Mar-01	21-Jan-03	57
1839IL/0168	PHASE II STUDY OF ZD1839 IN RECURRENT OR METASTATIC SQUAMOUS CELL CANCER OF THE HEAD AND NECK	13-Mar-01	22-Jun-04	52
1839IL/0169	A PHASE I/RANDOMIZED PHASE II TRIAL OF OXIPLATIN WITH OR WITHOUT ZD1839 IN PATIENTS WITH ADVANCED COLORECTAL CARCINOMA	31-Dec-01	21-Jan-03	14
1839IL/0170	ZD1839 FOR THE TREATMENT OF PROGRESSIVE MALIGNANT ASTROCYTOMA OR GLIOBLASTOMA AND RECURRENT OR PROGRESSIVE MENINGIOMA: A PHASE I COMPONENT FOR PATIENTS RECEIVING EIAEDS	31-Dec-01	ongoing	96
1839IL/0171	A PHASE II STUDY OF ZD1839 IN PATIENTS WITH MALIGNANT MESOTHELIOMA	30-Sep-01	17-Sep-03	44
1839IL/0174	A RANDOMIZED PHASE II TRIAL OF TWO DOSE LEVELS OF ZD1839 IN PATIENTS WITH RECURRENT COLORECTAL ADENO- CARCINOMA	9-Sep-01	4-Nov-03	115

23. The Investigator Sponsored Studies, with the exception of Study No. 1839IL/0156, were carried out under a **master Clinical Trials Agreement with the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD)**. The introduction to this Agreement notes the objective of the collaboration between DCTD and the pharmaceutical industry in the development of new anti-cancer agents:

> "The Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), recognizes the importance of the pharmaceutical industry in the

clinical development of new anti-cancer agents. DCTD wishes to foster collaboration with industry whenever possible. As part of its mission to improve cancer care, DCTD shares with industry the important goal of defining the contribution of a new drug or biologic in the treatment of cancer. DCTD therefore recognizes and supports the need of a private sponsor to focus at the appropriate time on clinical trials which lead to a New Drug Application (NDA) or a Biological License Application (BLA) since an NDA and a BLA, once approved, are the vehicles through which new anti-cancer therapies become widely available to cancer patients. Thus DCTD considers it appropriate for the investigators sponsored by DCTD to do clinical trials of interest to, and partially supported by a pharmaceutical firm, provided that the trials have scientific merit and are consistent with the overall goals of the investigators and DCTD.

"Inasmuch as DCTD coordinates a large volume of clinical research with new anti-cancer agents, industry recognizes DCTD's need to be aware of industry's plans for the clinical development of new agents of mutual interest, particularly if a pharmaceutical firm wishes to utilize the resources of the DCTD-supported clinical trials mechanism. Industry also recognizes the necessity of preserving the spirit of free and open inquiry among clinical investigators."

24. This Clinical Trials Agreement, which was in effect more than one year prior to the effective filing date of the subject application, provided in part as here relevant with respect to the co-development of ZD1839 (Agent) by Collaborator (AstraZeneca) and DCTD, as follows:

24.1. **With respect to the Definitions**:

"'*Clinical Brochure*' means a document containing all the relevant information about the drug, including preclinical pharmacology, preclinical toxicology, and detailed pharmaceutical data. Also included, if available, is a summary of current knowledge

about pharmacology and mechanism of action and a full description of the clinical toxicities.

* * * * *

"'*Proprietary/Confidential Information*' means confidential scientific, business or financial information, provided that such information:

> "is not publicly known or available from other sources who are not under a confidentiality obligation to the source of the information;
>
> "has not been made available by its owners to others without a confidentiality obligation;
>
> "is not already known by or available to the receiving Party without a confidentiality obligation;
>
> "does not relate to potential hazards or warnings associated with the production, handling or use of the subject matter of this Agreement; and

"If any one or more of the above provisions of this definition are not met, the relevant information shall no longer be considered proprietary/confidential."

24.2. **With respect to Planning of Clinical Trials with Agent:**

"The plan for the clinical development of Agent under this Agreement will be a collaborative undertaking by Collaborator and DCTD and will be limited to the clinical trial protocols set forth in Exhibit B, attached hereto and incorporated herein, and any additional DCTD-sponsored clinical protocols mutually agreed upon by DCTD and Collaborator. ... All studies sponsored by DCTD using Agent will be

mutually agreeable to Collaborator and DCTD, in as much as Collaborator will have final authority over the provision of Agent to DCTD."

24.3. **With respect to Protocols:**

"A general plan for the clinical development of Agent, as contemplated herein, will be established by both parties through the Steering Committee. Based on this plan, protocol LOIs will be solicited from investigators. Each clinical research protocol received by DCTD will be forwarded to Collaborator for review and comment approximately two weeks before it is reviewed by the Protocol Review Committee (PRC) of CTEP. Comments from Collaborator received by CTEP before the PRC meeting will be discussed by the PRC, will be given due consideration, and will be incorporated into the protocol absent good cause. Comments from either Collaborator of the CTEP staff that are agreed upon in the PTC meeting will be formatted as a consensus review, which is returned to the investigator for necessary and/or suggested changes before the protocol can be given final approval and submitted to the FDA. A copy of the final approved protocol will be forwarded to Collaborator at the same time it is submitted to the FDA. In summary, under this Agreement, Collaborator will co-develop with DCTD a clinical plan for the overall development of Agent and receive copies of all DCTD-sponsored protocols both before review and after approval. The clinical plan will be limited to the clinical protocols set forth in Exhibit B, and any additional DCTD-sponsored clinical protocols as mutually agreed upon by DCTD and Collaborator. Subject to the terms of Article 6 [Drug Information and Supply], all protocols sponsored by DCTD using Agent must be mutually agreeable

to Collaborator and DCTD, in as much as Collaborator will have final authority over the provision of its agent to DCTD. NCI standard protocol language, a copy of which is attached hereto as **Exhibit A** [excerpts presented below] and incorporated herein by this reference, will be incorporated in all protocols sponsored by DCTD using Agent within the scope of this Agreement."

24.3.1. **Exhibit A provides in part as relevant here:**

"Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators."

* * * * *

"Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. ... No publication,

manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information."

24.4. **With respect to Drug Information and Supply:**

"Collaborator agrees to provide to DCTD, without charge, Agent in sufficient quantity to complete the protocols sponsored by DCID, that have been mutually agreed upon by Collaborator and DCTD. ... Furthermore, Collaborator agrees to permit DCTD to provide Agent, or unformulated analytical grade Agent or metabolites, if available, to DCTD extramural investigators for the development of analytical assays or ancillary correlative studies conducted in conjunction with protocols approved by DCTD and agreeable to Collaborator in accordance with the provisions of Articles 2 and 4. All protocols sponsored by DCTD using Agent must be mutually agreeable to Collaborator and DCTD, in as much as Collaborator will have final authority over the provision of its agent to DCTD."

24.5. **With respect to Data Rights:**

"The data generated under this Agreement are considered the property of the party that generates the data. Generally, data generated in trials sponsored by DCTD with funding through Grants or Cooperative Agreements are considered the property of the Extramural Principal Investigator or the Cooperative Groups, respectively. Generally, the data generated in trials sponsored by DCTD with funding through Contracts are the property of DCTD. The data generated by NCI intramural principal investigators are the property of NCI. It is the intention of the NCI that except as may be required by the Freedom of Information Act or other applicable law or court order that

Collaborator shall have complete and exclusive access to all the data and results generated under this Agreement that are in the possession and control of DCTD. This includes all data received from DCTD-sponsored extramural clinical trials, which are generally made available to DCTD in summary form (Summary Data), compilations of which are included in the Annual Report to FDA. All the data and results generated under this Agreement that are in the possession and control of DCTD will be made fully and exclusively available to Collaborator for its own analyses and for its application for FDA approval. If there are additional costs to the investigator for providing such data, the investigator shall be reimbursed for the reasonable additional costs by Collaborator in a manner to be negotiated by investigator and Collaborator, after discussing the data required with the CTEP contact (Dr. Sherry Ansher, Regulatory Affairs Branch, Telephone Number 301-496-7912)."

24.6. **With respect to Proprietary/Confidential Information:**

"Any preclinical or formulation data considered Proprietary/Confidential Information by Collaborator will be treated as such by DCTD. Collaborator should state in advance what information it considers proprietary/confidential and DCTD can accept, or decline to accept, information so designated. DCTD shall treat in confidence any of Collaborator`s written information that is stamped "CONFIDENTIAL" and oral information which is reduced to writing and marked "CONFIDENTIAL" within thirty (30) days of such disclosure. The obligation to maintain the confidentiality of Collaborator's Proprietary/Confidential Information shall expire at the earlier date when the information is no longer Proprietary/Confidential Information as defined in

Article 1 [Definitions] or three (3) years after the expiration or termination of this Agreement, unless Collaborator informs DCTD that the Proprietary/Confidential Information is still secret and confidential, and DCTD concurs, in which ease the obligation hereof shall extend for a further period of two (2) years. Such Proprietary/Confidential Information shall not include information or data exempted from the definition of "Proprietary/Confidential Information" under Article 1. Collaborator shall disclose Proprietary/Confidential Information only for the purposes described in the Agreement and such information shall only be used for the purposes described in this Agreement. Primary data relating to sensitive laboratory studies will, upon request by Collaborator, be returned to Collaborator by DCTD. However, summaries of all such studies will be retained in the DCTD files. It is the intention of the NCI that except as may be required by the Freedom of Information Act or other applicable law or court order that all data derived from clinical trials at a DCTD-sponsored institution will be made fully, and exclusively available for use by Collaborator in obtaining regulatory approval. The data will be made available to DCTD in summary form (Summary Data). The Confidential Disclosure Agreement executed by and between the Parties on February 24, 1999 is attached hereto as **Exhibit C** [excerpts presented below] and incorporated herein by this reference."

24.6.1. **Exhibit C provides in part as relevant here:**

"WHEREAS, Company [Zeneca, now AstraZeneca] has certain confidential and/or proprietary information relating to Zeneca's proprietary agents ZD1839 ...

for the possible treatment/prevention of cancer (hereinafter referred to as the "Confidential Information"); and

"WHEREAS, Company's Confidential Information will be provided to NCI in order to determine the desirability of entering into an agreement relating to a possible preclinical and/or clinical collaboration for the development of such Confidential Information.

"NOW, THEREFORE, in consideration of the premises and mutual covenants contained herein, the Parties hereto agree as follows:

"1. Company shall disclose and transmit Confidential Information to NCI solely for the purpose of and in sufficient detail to enable NCI to make the determinations set forth above.

"2. NCI agrees to employ all reasonable efforts to maintain the Confidential Information hereunder secret and confidential, such efforts to be no less than the degree of care employed by NCI to preserve and safeguard it's own confidential information. The Confidential Information shall not be disclosed, revealed, or given to anyone by NCI except employees of NCI who have a need to have the Confidential Information in connection with NCI's evaluation, and who have entered into a secrecy agreement with NCI under which such employees are required to maintain confidential and secure the Confidential Information provided to them in the course of their employment. Such employees shall be advised by NCI of the confidential nature of the

Confidential Information and that the Confidential Information shall be treated accordingly.

"3. It is hereby acknowledged by Company that NCI shall incur no liability merely for examining and considering the Confidential Information; however, NCI agrees that it will not use the Confidential Information for any purpose except as set forth herein, provided that such limitation shall not apply to the NCI if and when a further signed agreement is first made providing the terms and conditions under which rights are to be acquired.

"4. NCI's obligations under Paragraph 2 and 3 above shall not extend to any part of the Confidential Information:

"(a) that can be demonstrated to have been publicly known at the time of disclosure; or

"(b) that can be demonstrated to have been in the NCI's possession prior to the disclosure; or

"(c) that becomes part of the public domain or publicly known by publication or otherwise, not due to any unauthorized act by NCI; or

"(d) that can be demonstrated as independently developed or acquired by or for NCI without reference to or reliance upon such Confidential Information; or

"(e) that is required to be disclosed by law, provided that NCI notifies the Company as soon as practicable and permits Company an opportunity to take such actions as it deems appropriate to avoid and/or minimize such disclosure.

"5. NCI's obligations under Paragraphs 2 and 3 shall extend for a period of three (3) years from the date of this Agreement, unless Company informs NCI that the Confidential Information is still secret and confidential, in which case the obligations of Paragraphs 2 and 3 hereof shall extend for a further period of two (2) additional years.

"6. All information to be deemed confidential under this Agreement shall be clearly marked "CONFIDENTIAL" by Company. Any Confidential Information which is orally disclosed or provided in some other form must be reduced to writing, marked "CONFIDENTIAL" by Company, and provided to NCI within thirty (30) days of such disclosure.

"7. It is understood that nothing herein shall be deemed to constitute, by implication or otherwise, the grant to NCI of any license or other rights under any patent, patent application or other intellectual property right or interest belonging to Company or as permitting NCI to unfairly obtain the right to use any Confidential Information which becomes publicly known through an improper act or omission on its part."

24.7. With respect to Publications and Commercialization:

"The DCTD investigators maintain the full right to present and publish the data at such time and place as they see fit, subject to the provisions of this Agreement.

Manuscripts reporting Clinical Data and Results of trials conducted within the scope of this Agreement or those to which Collaborator has specifically committed financial resources should have advisory review and comment prior to submission for publication to assure that Proprietary/Confidential Information is protected. Collaborator will review manuscripts prior to submission for all protocols within the scope of this Agreement. The amount of time required for the review shall not exceed thirty (30) days. The publication or other disclosure shall be delayed for up to an additional thirty (30) days upon written request by either Party to this Agreement as necessary to preserve U.S. or foreign patent or other intellectual property rights.

"Abstracts presented by NCI investigators will be sent to NCI's Regulatory Affairs Branch for forwarding to Collaborator as soon as they are received, preferably prior to submission, but prior to presentation or publication for courtesy notification and to preserve U.S. or foreign patent or other intellectual property rights. No publication or manuscript shall contain Collaborator's Proprietary/Confidential Information."

25. **Investigator Sponsored Study No. 1839IL/0156,** was carried out under a Clinical Study Agreement that provided in part as here relevant:

25.1. **With respect to Scope of Work:**

"Institution and Principal Investigator shall conduct the clinical study 'A Non-randomized, Open-label Phase II, Multi-center Trial of ZD I839 (Iressa™) 500mg Daily in Patients With Advanced Breast Cancer' (the "Study") in accordance with this Agreement, Protocol Number 18391L/0156 incorporated by reference herein and as may be amended (the 'Protocol'), good clinical and medical practice, and all applicable laws, rules, regulations and guidelines relating to the conduct of clinical investigations, including, without limitation, 21 CFR Parts 50, 54, 56, and 312 (the 'Applicable Laws'). For purposes of this Agreement, the term 'Institution' shall include all other employees, executives, officers, directors, faculty, staff, and other authorized agents of Institution."

25.2. **With respect to Ownership and Control of Study Drug:**

"All Study Drug supplied to Institution shall remain the exclusive property of AstraZeneca until administered or dispensed to Subjects during the course of the Study. The Study Drug shall only be used as described in the Protocol in compliance with Applicable Laws. Upon termination or completion of the Study, Institution shall, at AstraZeneca's direction, either return to AstraZeneca or dispose of any quantities of unused Study Drug, in accordance with AstraZeneca's instructions. Institution shall maintain complete and accurate records relating to the disposition of the Study Drug supplied to Institution."

25.3. **With respect to Records; Reports; and Regulatory Assistance:**

"(a) Institution shall prepare, maintain, and retain complete, current, accurate, organized and legible Study Documentation in a manner acceptable for the collection of data for submission to, or review by, the FDA and other regulatory or governmental authorities, and in full compliance with the Study and all Applicable Laws. For purposes of this Agreement:

"(i) 'Study Documentation' includes all records, accounts, notes, reports and data relating to the Study, whether in written, electronic, video or other tangible form.

"(ii) 'Source Documents' includes all recorded original observations and notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the Study, regardless of form.

"(b) Institution shall provide to AstraZeneca documentation verifying review and approval by an Institutional Review Board approved by Institution ("IRB"), of the Protocol, the Investigator's Brochure, and the information to be provided to potential subjects of the Study to secure their informed consent; original case report farms for each Subject participating in the Study; and such other reports when and as required by the Study or Applicable Laws. Institution shall provide the final data and reports required by the Study no later than the Data Completion Date set forth in Exhibit A or such later date as AstraZeneca may require.

"(c) At the request and expense of AstraZeneca, Institution and Principal Investigator shall (i) assist AstraZeneca in the preparation and submission of

investigational new drug applications, new drug applications, and any other premarket application relating to the Study and marketing applications relating to the Study Drug, and (ii) attend meetings with the FDA and other regulatory or governmental authorities regarding such applications and the associated approvals."

25.4. **With respect to Ownership of Equipment, Intellectual Property and Work Product:**

"All materials, documents, data, software and information supplied to Institution by AstraZeneca or prepared, developed or generated by or on behalf of Institution, including but not limited to Source Documents and Study Documentation (excluding records which are solely patients' medical records) in connection with the Study or the performance of its obligations under this Agreement (the "Property") shall be and remain the sole and exclusive property of AstraZeneca. Any such Property shall be delivered to AstraZeneca by Institution immediately upon demand. For purposes of this Section 14, "AstraZeneca" shall include any designee of AstraZeneca, including any direct or indirect affiliate of AstraZeneca plc."

25.5. **With respect to Confidential Information:**

"(a) For purposes of this Agreement, "Confidential Information" means any information of AstraZeneca, whether of a technical, business or other nature, including, but not limited to, information that relates to materials supplied to Institution by AstraZeneca, AstraZeneca's trade secrets, products, promotional material, developments, proprietary rights or business affairs, together with any Inventions, Work Product and all other information collected, prepared, developed or generated by Institution, Principal Investigator and any other person pursuant to this Agreement, including this Agreement. Confidential Information does not include any information that:

"(i) Institution and/or Principal Investigator can prove was known to it prior to the date of this Agreement and was not subject to any confidentiality restrictions;

"(ii) Institution and/or Principal Investigator can prove was lawfully obtained from a third party without any obligation of confidentiality; or

"(iii) Is or becomes part of the public domain through no act or violation of any obligation of Institution and/or Principal Investigator.

"(b) For a period of ten (10) years after the expiration or termination of this Agreement, Institution and/or Principal Investigator shall not, without AstraZeneca's prior written consent or as may be permitted by this Agreement, disclose to any third party any Confidential Information, and shall use such Confidential Information solely for purposes of performing its obligations under this Agreement. Institution shall restrict the dissemination of Confidential Information to only those persons within its organization who have a need to know, and shall ensure that they are aware of the obligation of confidentiality required by this Agreement and are similarly bound, Institution and/or Principal Investigator shall use at least the same care and discretion in maintaining the confidentiality of the Confidential Information as it uses with its most sensitive confidential information. Institution and/or Principal Investigator shall notify AstraZeneca immediately upon Institution and/or Principal Investigator's discovery of any loss or compromise of the Confidential Information. Upon the termination or expiration of this Agreement or upon AstraZeneca's earlier request, Institution and/or Principal Investigator shall promptly return to AstraZeneca all Confidential Information.

"(c) Notwithstanding subparagraph (b) above, if Institution and/or Principal Investigator are legally required to disclose Confidential Information and/or results of the Study, Institution and/or Principal Investigator shall promptly notify AstraZeneca in writing no less than three (3) business days prior to making the required disclosure. Institution and/or Principal Investigator shall craft such disclosure as reasonably requested by AstraZeneca so that such disclosure shall contain only such Confidential Information as is required by Applicable Laws. Nothing contained herein shall prohibit Institution and/or Principal Investigator from immediately disclosing results of the Study to the extent necessary to prevent or mitigate a serious health hazard, provided, however, that Institution and/or Principal Investigator shall notify AstraZeneca prior to making such a disclosure, and immediately after it has made such a disclosure."

25.6. **With respect to Rights of Publication:**

"(a) Institution and Principal Investigator understand that the Study is being conducted as part of a multi-center clinical trial, that data from all centers will be pooled and analyzed, and agree that disclosure of data from a single site may be misleading. Therefore, Institution and/or Principal Investigator shall not publish or present information related to the Study without the prior written permission of AstraZeneca. AstraZeneca may withhold permission if a publication or presentation (i) is in violation of Section 15 hereof, (ii) is not consistent with academic standards, (iii) is false or misleading, or (iv) is for commercial purposes.

"(b) Institution and/or Principal Investigator shall submit a copy of any proposed manuscript, abstract, presentation or other document to AstraZeneca for review and comment at least sixty (60) days prior to its submission for publication or presentation. No publication or presentation with respect to the Study shall be made unless and until all AstraZeneca comments on the proposed publication or presentation have been addressed to AstraZeneca's satisfaction and any information determined by AstraZeneca to be Confidential Information has been removed. If requested in writing by AstraZeneca, Institution and/or Principal Investigator shall withhold material from submission for publication or presentation for an additional one hundred twenty (120) days to allow for the filing of a patent application or the taking of other measures to establish and preserve AstraZeneca's proprietary rights. To the extent that any provision of this Section 16 may be inconsistent in any respect with any statements about publication policy set forth in the Protocol, the provisions of this Section 16 shall control.

"(c) Institution and Principal Investigator agree that, if either publishes the results of the Study, AstraZeneca is hereby granted an irrevocable, royalty-free license to make and distribute copies of such publication under any copyright privileges that Institution or Principal Investigator may have. AstraZeneca also shall have the right to publish independently the results of the Study."

Study Protocols

26. The Protocols referenced with respect to the above-listed Clinical Trials/Studies provided details of, *inter alia*, the:

- criteria for the selection and screening for eligibility of subjects for entry into the trial, as well as exclusion criteria;
- route, dose and regimen for administration of the respective drugs to individual subjects;
- procedures for drug accountability, including maintenance of accurate records on receipt and disposition of investigational materials, and return or destruction of any unused drug;
- frequency and procedures for clinical and laboratory evaluations;
- regular recordation of data on case report forms, record retention and submission of records to AstraZeneca; and
- trial monitoring and data verification by representatives of AstraZeneca.

27. As particularly relevant here, the Protocols also required very strict control and accountability with respect to the investigational drug (ZD1839), to insure that it was used only in accordance with the protocol, that all drug product was accounted for, and that any unused drug was returned to AstraZeneca or destroyed. For example:

27.1. **The Protocol for AstraZeneca Sponsored Trial No. 1839IL/0011 provided:**

"Storage"

"The tablets must be stored in a lockable storage area, below 30°C (86°F) and protected from light."

* * * * *

"Drug Accountability"

"The investigational products are to be prescribed by the investigator or subinvestigators named in form FDA- 1572. Under no circumstances will the investigator allow the investigational drug to be used other than directed by the protocol in subjects enrolled and continuing to meet stated criteria for continuing.

"The trial treatment(s) must be used only as directed in the protocol. Records of overall dispensing and returns will be maintained by each center, separately from the case report forms (CRFs) recording the treatment dispensed to individual subjects.

Subjects must return all unused medication and empty containers to the investigator, who will retain these until they are collected by Zeneca Pharmaceuticals' authorized personnel, along with any trial treatments not dispensed.

"The investigator must maintain accurate records accounting for the receipt of the investigational products (Zeneca provides a copy of the Investigational Product Shipping Order for this purpose) and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug was dispensed, the quantity and date of dispensing, and any unused drug returned to the investigator. In this out-subject trial, subjects must return all unused drugs to the investigator. This record is in addition to any drug accountability information recorded on the CRF's. At the termination of the trial or at the request of the sponsor, the investigator must return any unused supplies to Zeneca. This return will be documented by using an Investigator Product Return Invoice supplied by Zeneca."

27.2. **The Protocol for Expanded Access Trial No. 1839IL/0050 it is provided:**

"Formulation, presentation, and storage"

* * * * *

"For US centers, all trial treatment will be stored in a lockable storage area, between 20-25°C (68-77°F), and protected from light."

* * * * *

"ZD1839 drug accountability"

"It is the investigator/institution's responsibility to establish a system for handling trial treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products from AstraZeneca Pharmaceuticals (or AstraZeneca's representative) are correctly received by a responsible person (e.g., a pharmacist)
- Deliveries are recorded
- Trial treatments are handled and stored safely and properly
- The drug is to be prescribed only by the investigator or sub-investigators named in Form FDA-1572
- Trial treatments are dispensed only to trial patients in accordance with the protocol
- Any unused trial treatment and empty bottles are returned to USI, 2084-900 Lake Industrial Court, Conyers, GA 30013.

"At the end of the trial, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the trial treatment was dispensed, the quantity and date of dispensing, and unused trial treatment returned to the investigator. This record is in addition to any drug accountability information

recorded on the CRFs. Any discrepancies must be accounted for on the appropriate form. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained for the Investigator File."

28. Patients as well as the Institutions and Investigators were made well aware of the investigational nature of the drug. These Protocols furthermore required that each subject be given appropriate information on the treatment prior to its commencement, including the experimental aspects of the treatment and the risks involved, and sign an informed consent form approved by AstraZeneca, and conforming to the requirements of 21 C.F.R. 50.20 *et seq.* , which requires as a basic element of informed consent, that each subject be provided with, *inter alia*, a "statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental." 21 C.F.R. 50.25(a)(1). For example:

28.1. **The Protocol for AstraZeneca Sponsored Trial No. 1839IL/0011 provided:**

"Formulation and presentation"

* * * * *

"Each bottle will have an investigational-use label permanently affixed to the outside stating that the drug is to be used only for investigational purposes."

* * * * *

"Informed consent"

"Zeneca must review and approve the proposed consent form before initiation of the trial. The proposed form must contain a full explanation of the possible advantages, risks, alternative treatment options, and availability of treatment in the case of injury, in accordance with the Federal Regulations as detailed in 21CFR 50. It should also indicate by signature that the subject, or where appropriate, legal guardian, permits representatives of Zeneca and the FDA access to relevant medical records.

"The investigator is responsible for obtaining written informed consent from potential subjects before performing any trial tests or assessments required by the protocol. A copy of the signed document will be given to the subject, and the original will be retained by the investigator with his/her copy of the record forms."

28.2. The Protocol for Expanded Access Trial No. 1839IL/0050 it is provided:

"Formulation, presentation, and storage"

* * * * *

"Each bottle of trial material will have an investigational-use label permanently affixed to the outside, stating that the drug is to be used only for investigational purposes."

* * * * *

"Informed consent"

"The investigator must explain the trial fully to the patient. A patient information sheet, giving details of the trial, will be provided for the patient to read and retain. [AstraZeneca's contract project manager] must be informed of any center-specific changes to the patient information sheet or consent form. Copies of the amended information sheet must be provided to [AstraZeneca's contract project manager] for approval and a copy retained in the Investigator File. After patients have had time to fully consider the information and have been encouraged to ask questions,

they will be asked to give fully informed consent by signing and dating a consent form. **Written, informed patient consent is mandatory**. All consent forms should be signed and dated by the investigator or his/her authorized representative. The patient will receive a copy of the signed and dated consent form (this can be a wet-ink signature or a photocopy). A signed curriculum vitae and investigator's authorization to inform patients must be provided for any physician signing the consent form as the investigator's representative. The investigator must ensure that the representative is fully informed regarding the trial. In the US, if the patient is unable to read or write, the consent forms should be marked in some manner by the patient and signed and dated by the investigator and an independent witness, to indicate that the patient apparently understood the information and consented freely. This would then be considered a signed consent. Direct access to patient notes for verification and auditing purposes will be required (see Section 10.3.2), and permission from each patient must be obtained as part of the consent process. Written consent must be obtained from the patient before **any** non-routine screening procedures are performed. "Consent forms will be reviewed at the trial center and retained by the investigator."

29. AstraZeneca (directly or through its contract project manager) also monitored the trials and documentation prepared to assure that appropriate records were prepared and maintained, and that AstraZeneca had full access thereto. The protocol provided that all documents relating to the trial were the confidential property of AstraZeneca, and reiterated the confidential property designation of the Investigator's Brochure (IB). For example:

29.1. **The Protocol for AstraZeneca Sponsored Trial No. 1839IL/0011 provided:**

"Record retention"

"All documents relating to the trial, including the protocol and the Investigator's Brochure, are the confidential property of Zeneca and should be regarded as such. Unused CRF's should be returned to Zeneca at the end of the trial by a method that is agreed with the CRA monitoring the trial."

29.2. **The Protocol for Expanded Access Trial No. 1839IL/0050 it is provided:**

"Record retention"
"All documents relating to the trial, including the protocol and the IB, are the confidential property of AstraZeneca Pharmaceuticals and should be regarded as such. Unused CRFs should be returned to AstraZeneca at the end of the trial by a method that is discussed with the CRA monitoring the trial."

Discussion

In evaluating the above circumstances in context of 35 U.S.C. § 102(b), the Examiner's attention is called to MPEP ¶ 2133.03 "Rejections Based on 'Public Use' or 'On Sale', and particularly MPEP ¶ 2133.03(a) "Public Use", section *B.* headed "*Use by Third Parties Deriving the Invention from Applicant.*" It is respectfully submitted that the above circumstances *do not* constitute a "public use" of the presently claimed invention under the criteria set forth in the MPEP, and as established by decisions of the Federal Circuit, because of the strict confidentiality and control imposed and maintained by AstraZeneca throughout the relevant trial periods. MPEP ¶ 2133.03(a)*B.* provides:

> **An Invention Is in Public Use If the Inventor Allows Another To Use the Invention Without Restriction or Obligation of Secrecy**
> "Public use" of a claimed invention under 35 U.S.C. 102(b) occurs when the inventor allows another person to use the invention without limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134, 218

> USPQ 976, 983 (Fed. Cir. 1983). The presence or absence of a confidentiality agreement is not itself determinative of the public use issue, but is one factor to be considered along with the time, place, and circumstances of the use which show the amount of control the inventor retained over the invention. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1265, 229 USPQ 805, 809 (Fed. Cir. 1986). See *Ex parte C*, 27 USPQ2d 1492, 1499 (Bd. Pat. App. & Inter. 1992) (Inventor sold inventive soybean seeds to growers who contracted and were paid to plant the seeds to increase stock for later sale. The commercial nature of the use of the seed coupled with the "on-sale" aspects of the contract and apparent lack of confidentiality requirements rose to the level of a "public use" bar.); *Egbert v. Lippmann*, 104 U.S. 333, 336 (1881) (Public use found where inventor allowed another to use inventive corset insert, though hidden from view during use, because he did not impose an obligation of secrecy or restrictions on its use.).

The clinical trials or studies conducted in human subjects did not constitute a "public use" under the definition thereof set out in the MPEP as developed by the courts. Prior to the release of any materials or formulations on which to carry out these studies, the institutions and/or investigators involved were required to sign an agreement whereunder strict confidentiality was required,[1] and all information provided to or developed by the institution/investigator during the course of such studies remained or became the property of AstraZeneca.[2] Throughout the Clinical Study Agreements, and the Protocols under which all of the clinical trials were conducted, AstraZeneca maintained full control over the use and disposition of the study materials or formulation that it provided to the institutions/investigators throughout the course of these studies, and the right to receive the data and records that were produced.[3] Moreover, each subject of these studies was fully informed of the experimental nature of the formulation and its use, as acknowledged in signed informed consent forms, and clearly did not have any basis to believe that the

[1] See, *e.g.*, paragraphs 13, 16.4, 17.3, 21, 24.1, 24.3.1, 24.6 and 25.5 above.
[2] See, *e.g.*, paragraphs 16.4, 17.3, 18.4 and 25.3 above.
[3] See, *e.g.*, paragraphs 16.1, 16.3, 17.1, 17.2, 18.1, 18.2, 24.2, 24.3, 25.4, 24.5, 27.1, 27.2, 29.1 and 29.2 above.

formulation or its use in the treatments was in the public domain or otherwise freely available.[4] Again, AstraZeneca received no payment for the formulation used in these studies, and these studies did not constitute a commercial exploitation of the formulation.

Therefore, under the case law as developed by the courts, and its application by the Patent and Trademark Office as set out in the above-quoted paragraph from the MPEP, it is respectfully submitted that the foregoing circumstances do not constitute a "public use" under 35 U.S.C. § 102(b).

Respectfully Submitted,
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[4] See, *e.g.*, paragraphs 27.2, 28.1 and 28.2 above.